TOBACCO INDUSTRY RESEARCH COMMITTEE

TIRC Grant #181

CONFIDENTIAL

Report No. 1

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An Evaluation of the Phenomenon of Tumor Growth Enhancement as an Assay for Carcinogens Among the Polycyclic Hydrocarbons and Related Compounds

Dear Dr. Hockett:

Thank you for your letter of October 28. I was wondering what you would want in the way of a report. Your request is a very good answer to my question.

It is difficult to say much about this project without referring to the details of a rather complex background. This I would like to provide in the form of my report to the U.S. Public Health Service, which is enclosed. As you can see, it covers the work through the first half of this year.

I would like to point out especially the sections on: 1) Effects of carcinogens on tumor growth -- page 5; 2) Quantitation of carcinogen enhancement effect -- page 6; 3) Effect of other carcinogens and related hydrocarbons -- page 7; 4) Transplantation of skin -- page 12; and 5) Studies in chemotherapy -- page 14. All of these refer to some newer aspects of the effect of carcinogens on transplantation.

In addition to the material in these sections, we are doing work on the standardization of the method. Because of occasional variation in the extent of tumor growth in normal mice -- and the consequent variation in "controls", against which our effect must be measured -- we conducted (and continue) some studies on the growth of different tumor lines in C3H, CBA, DBA/2, and various hybrids. In brief, the behavior of the tumor in DBA/2 mice seems to depend upon the mice in which it was previously carried. We have tested three tumor (6C3HED) lines from Rutgers and three of our own in a variety of situations. It is too early to go into much detail, except to say that the tendency is for the controls to diverge more from carcinogen treated animals. It has been occasional contention of Dr. Hauschka that "anything" grows in DBA mice -- and therefore, this effect is not surprising. Our findings would indicate that you have to control conditions carefully to get this tumor to grow at all in these mice. While this may provide a more clear-cut effect for strong carcinogens, it cuts down on sensitivity for weak ones.

Since the compounds we want to test are so valuable (and scarce), I have hesitated to let them go out until the test could provide reliable and reproducible quantitative effects. The alternative is to test everything at the same time -- which would require an immense number of mice. We are indeed building up toward a larger group, but I trust this other problem will soon be resolved.

It may be of interest to you to know that Dr. Fred Bock has written to me recently about his work with this system. He complains that his growth in DBA mice is too slow -- although he easily confirms the basic findings. I have written to him about my observations on the tumor and its origins. He is esperiencing another aspect of this same problem.

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The other part of our work concerns the synthesis and procurement of carcinogens and their analogs. With the help of Dr. Osdene we have synthesized good quantities of six compounds and will probably have 2-3 more before the end of the year. These are all benzacridines of varying levels of carcinogenicity. We have also purchased 10 additional members of this series from the Light Company in England.

In addition, we have obtained a large group of methylated benzanthracenes, benzphenanthrenes, benzpyrenes, crysenes, and cholanthrenes.

Many of these are available through the collaboration of Dr. Ralph S. Becker of the University of Houston. He has a wonderful collection of high purity standards for his work on spectral properties. He is eager to find a reliable biological test to compare with his physical findings. He was referred to me by the N.C.I., and we should both profit.

We will compare the physical properties of these compounds with 1) a standardized classical technique (32 weeks of skin painting), and 2) the tumor enhancement effect.

This will permit me to make my own comparisons of effect, rather than to rely upon the data in a literature of unknown variability.

Becker has found a very good correlation between the energy difference between two electronic absorption band maxima and published carcinogenesis. Other emission characteristics (fluorescence, phosphorescence, etc.) are providing additional information of value. But the biological data lack the quantitativeness of his observations -- and we hope that I can provide such quantitation with the present study.

To sum up, we have made progress in several directions, but this study will take longer than I had anticipated. However, the present developments indicate that we may come out with more valuable data than was previously possible.

If you require more details of my data or Becker's findings, I will be happy to provide them.

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